PATENT
MSB-7213

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	PETRA BOYLE GAYLE D. WETZEL KENNETH J. LEMBACH	DECLARATION UNDER 37 C.F.R. § 1.132
Serial No.:	08/026,957	EXAMINER: R. D. BUDENS
Filed:	March 5, 1993	ART UNIT: 1806
For:	HUMAN ANTI-TNF ANTIBODIES	

Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

I, Matthias Wabl, declare as follows:

1. I have been awarded a Ph.D. degree in Biology from the Max Planck Institute, Berlin and have approximately 16 years experience in making cell lines that express monoclonal antibodies.

2. UTILITY: The above-entitled Patent Application is concerned with human monoclonal antibodies that specifically bind to TNFα. I understand the Examiner has rejected the claims in that Patent Application on the ground that Applicants have not mentioned specific uses for the antibodies. In my opinion, a variety of specific uses would immediately be obvious to a person skilled in the art. For example, it is well known that any monoclonal antibody, once generated, can be used in a variety of immunoassays which would be inherently useful for not only research but as diagnostic tools. As shown in the enclosed catalog copies, anti-TNF antibodies are commercially available, thus confirming their obvious utility.

In addition, I am aware of clinical studies currently in progress using murine monoclonal antibodies that bind to TNFα. See the

attached copy of a Poster Session No. 696, presented at the 3rd ICAAC meeting, October 17, 1993. See also the enclosed copy of an article that appeared in the July 15, 1994, Genetic Engineering News showing that Chiron/Miles is developing an anti-TNF monoclonal antibody for the targeting of TNFα.

3. ENABLEMENT: I understand the Examiner states it is not clear from the teachings of the Patent Application that one of ordinary skill in the art could make other human anti-TNFα monoclonal antibodies that bind specifically to TNFα without undue experimentation. I have reviewed the work leading to the Applicants' patent claims and believe that one skilled in the art, given the disclosure of the Patent Application and a related publication, Cellular Immunology, 152, 569-581 (1993), copy enclosed, could duplicate the Applicants' work and generate other cell lines that express human monoclonal antibodies that bind specifically to TNFα without undue experimentation using known screening techniques.

The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States code and that such willful false statements may jeopardizethe validity of the Application or any patents issuing thereon.

July 20, 94
Date

Matthias Wabl
Matthias Wabl, Ph.D.

3rd ICAAC
Oct 17-20 '93

Session 64. *Poster*
IMMUNE MEDIATORS
Tuesday, 10:30 A.M.

693 Placebo (Pla) Controlled Study of Ampligen® (AMP) in HIV Disease: Improvement in CD4 Level and Delayed Type Hypersensitivity (DTH). K. THOMPSON[*1], D. STRAYER[2], P. SALVATO[3], N. KLIMAS[4], A. MOLAVI[2], A. HAMILL[5], W. CARTER[1]. [1]HEM Pharmaceuticals Corp., Phila, PA; [2]Hahnemann University Hospital, Phila., PA; [3]CFIDS Center, Houston, TX; [4]VA Medical Center, Miami, FLA; [5]Nelson-Tobedo Clinic, Dallas, TX.

CD4 lymphocyte levels are an important surrogate marker for HIV disease progression. DTH response, a marker of in vivo immune function, has also been reported to predict HIV progression and survival independently of CD4 count (Blrx, et al, 1989, V Int. Congress AIDS, Montreal pQ, Th.B.P.155; Gordin, et al, 1992, Prog. Abstr. 32nd ICAAC, Anaheim CA, p. 335). The effect of AMP on these two endpoints was examined in a 48 week, double-blind, Pla-controlled study. 36 AZT-treated (≥ 5 months), HIV+ patients (pts) with CD4 levels of 100-500 were stratified by baseline CD4 and AZT usage and randomly assigned IV infusions of 400 mg AMP BIW (n=10); 700 mg AMP BIW (n=12); or Pla BIW (n=14). All Pts continued AZT therapy (300-500 mg/day). The groups were well-matched at baseline for sex, age, CD4 level, and duration of AZT therapy. 79% Pla and 73% AMP pts completed the study (p=1.0). Logistic regression analysis revealed that AMP-treated pts had a greater chance of positive DTH reactivity post-treatment than did Pla pts (p =.042). During the first 6 months, AMP pts reported fewer/less severe episodes of night sweats (p<.005). AMP treated pts that entered the study with CD4 counts > 300 (n=9) lost significantly fewer CD4 cells than Pla (n=6) over the course of the study (p=.04); AMP pts with CD4 < 300 did not differ from placebo. As part of a cross-over design, 7 of 11 eligible Pla pts began AMP therapy with resultant increased mean CD4 (p=.02) and DTH (p=.04) responses. These results indicate that AMP therapy modulates positively two markers of HIV disease progression and survival.

694 Long-term follow-up of 2 adenosine deaminase deficient patients treated with polyethylene glycol modified adenosine deaminase (PEG-ADA). WALCOTT DW[1]*, WILMAN BC[1], SORENSEN RU[2]. Departments of Pediatrics, Louisiana State University Medical Centers at Shreveport[1] and New Orleans[2], Louisiana.

Two unrelated black infants with severe combined immunodeficiency due to adenosine deaminase deficiency were started on PEG-ADA treatment shortly after diagnosis in the first 6 months of life. No HLA-identical donors were available for these patients. PEG-ADA, 30 Units/kg/week, has been well tolerated by both patients. There was a prompt clinical improvement coinciding with correction of biochemical abnormalities and increased immune function in both patients. Both were discharged from the hospital shortly after initiation of treatment, and both have led an unrestricted life at home since then. Patient 1 has completed 3 years on PEG-ADA, and patient 2 has completed 2 years on PEG-ADA. Growth and development has been normal. Patient 1 had varicella and Coxsackie virus B hepatitis, and developed persistent protective antibody titers against these viruses. Patient 2 has had four episodes of otitis media and developed onychomycosis of the fingernails that required a course of griseofulvin to resolve. Patient 1 developed a prominent thymic shadow by the 3rd month of PEG-ADA treatment, suggesting migration of T cell precursors through the thymus. For these two patients, enzyme replacement has offered an effective form of treatment for an otherwise fatal immunodeficiency.

695 Long-term Post-hospital Survival after Sepsis: Influence of Antien[illegible]body (E5). T.M. PERL*, L. DVORAK, C.M. FU, R.P. WENZEL. U[illegible] of I[illegible] College of Medicine, Iowa City, IA.

Because clinical efficacy trials for anti-endotoxin therapy evaluate mortality at 1 month and because short-term survival does not translate to long-term survival, we evaluated post-discharge survival of 100 septic patients entered in a double-blind, placebo-controlled efficacy trial of monoclonal antiendotoxin antibody (XOMEN-E5) between 12/86 and 12/90 at our institution. Beginning in 5/92, we contacted all known survivors. We found that 59 deaths occurred (29/50 (58%)-drug group (E5) vs 30/50 (60%)-placebo group). Thirty-three (55%) patients died within the first month of the septic episode, 6 (10%) died within 3 months, and 4 (6%) died within 6 months. Five patients died within 1 year, 6 within 2 years and 4 within 3 years. An additional patient died 5 years after the initial sepsis. We examined which factors predicted long-term survival (up to 5 years). The largest univariate hazard ratios (HR) were associated with severity of underlying disease as classified by McCabe (rapidly fatal: HR=27.4, p=0.0001 and ultimately fatal disease: HR=8.3, p=0.024). Thus, the mortality rate of patients with rapidly or ultimately fatal underlying diseases was 27.4 and 8.3 times greater than that of patients with non-fatal disease. Age and weight had low, but significant HRs of 1.03 (p=0.0004) and 1.02(p=0.03). The presence of infection-associated morbidities predicted long-term survival; disseminated intravascular coagulation (HR=2.2, p=0.008), shock (HR=2.4, p=0.002), central nervous system dysfunction (HR=2.5, p=0.0008). Having adult respiratory distress syndrome and receiving E5 did not affect survival (p=NS). Sex, positive cultures from blood or other sterile body sites, or admission to ICU was not significant by univariate analysis. Multivariate models will be developed. Our data show that 45% of deaths occur after clinical trials are terminated. Important outcomes may be missed if clinical trials only use a1 month follow-up.

696 Monoclonal Antibody to Human Tumor Necrosis Factor (TNF MAb): Multi-center Efficacy and Safety Study in Patients with the Sepsis Syndrome. J. WHERRY, R. WENZEL,* R. WUNDERINK, H. SILVERMAN, T. PERL, S. NASRAWAY, H. LEVY, R. BONE, R. BALK, R. ALLRED, and the TNF MAb Study Group

TNF MAb (Bay x 1351) is a murine monoclonal antibody raised against human tumor necrosis factor. In experimental models it has been shown to be effective in protecting animals from the morbidity and mortality associated with sepsis induced by Gram Negative Bacteria or Staphylococcus aureus. To evaluate the efficacy and safety of TNF MAb in patients with sepsis syndrome, a large multi-center 3 arm clinical trial was conducted in 31 hospitals in North America. Patients with sepsis were prospectively stratified by shock/non-shock and randomized to receive a single intravenous dose of 15 mg/kg TNF MAb, 7.5 mg/kg TNF MAb, or placebo (0.25% human albumin). All patients received standard medical and surgical care and were closely followed with clinical and laboratory measures of efficacy and safety; survival or non-survival was determined over the 28 day study period.

After the first 800 patients were enrolled a planned interim analysis was performed using the intent-to-treat principle. Based only on preliminary survival data it was concluded that if the study were to continue as initially designed there would be insufficient power to support efficacy of TNF MAb at either dose, for all sepsis syndrome patients. However, among shock patients there was a trend towards efficacy with lower mortality rates in both active treatment arms with the greatest effect seen in the 15 mg/kg arm. Among non-shock patients TNF MAb did not appear beneficial.

The study is now complete and the full database for all 971 infused patients is being finalized. Comprehensive results will be presented.

697 Double-blind, Randomized Comparison of the Safety Profile of Granulocyte Macrophage Colony Stimulating Factor (GM-CSF) vs Recombinant Granulocyte Colony Stimulating Factor (G-CSF) in Advanced HIV Infected Patients (P) with Neutropenia. P. HERMANS*, P. FRANCHIOLY, N. CLUMECK. St Pierre University Hospital, Brussels, Belgium.

This pilot study was initiated to determine the toxicity profile of 2 CFSs for acute salvage therapy in advanced HIV P with an absolute neutrophil count (ANC) < 1000/mcl. Starting daily dose was 1mcg/kg by subcutaneous route. The target value for response was defined as an ANC > 1000/mcl. Results: 12 P were enrolled in each arm between 01/92 and 08/92. Demographic data, clinical background and ANC at baseline were similar for P with GM-CSF and G-CSF. Haematologic response was achieved in 9/12 and 12/12 respectively after a median of 3 days. Toxicity profile is summarized on the following table:

Adverse events (AE)	GM-CSF	G-CSF	P value
Fever	7	1	P<0.05
Flulike/myalgia	3	1	NS
Bone pain	0	1	NS
Skin reaction	1	0	NS
Eosinophilia >\20%	3	0	NS
At least one AE	10	1	P<0.001

We conclude that for an efficacy at least similar, G-CSF appears significantly better tolerated when compared with GM-CSF in neutropenic HIV patients.